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09/912,163	07/24/2001	Klaus Fuchs	1/1143	3975

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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	

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7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/912,163	Applicant(s) Klaus Fuchs et al
	Examiner SUDHAKER PATEL,D.Sc.Tech.	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 7, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 6 dated 5/7/03 is acknowledged.

Claims 1-8 are related to compounds. Claims 9-16 are related to quaternary ammonium compounds. Claims 17,18 are composition claims. Claims 19-24 are method of use claims. Claims 25-29 are process of making claims. Therefore, the claims in this application are the claims 1-29.

The typographical mistake of reciting claims 1-39 has been corrected in the earlier office communication paper # 5 dated 9/27/02.

I. *Election/Restriction*

Applicant's election without traverse of invention of Group I and species of Example 13 in Paper No. 6 is acknowledged.

Since Claims 1-29 link with other invention, this application will be examined bearing in mind the subject matter and species of Example 13 (as recited on page 31) of specification as elected by the applicants only.

The election/restriction is deemed to be proper, and is made FINAL.

II. *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Applicants claim foreign priority based on DE 10040901.6 dated 8/18/2000, but the definition of component X on page 2 is not the same as X definition recited in instant application page 60 line 19. This will amount to addition of new matter.

Additionally, applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

However, domestic priority date according to U. S. Application Sr. No. 09912163 filed 7/24/2001 would be considered.

III. *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8,9-16,17,26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

(A). Claims 1,9 recite : " Compound of Formula 1 or a quaternary ammonium compound of Formula 1-Y respectively or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof".

Claims read on to acid addition salt(s) at more than one basic groups e.g. N or NH. Although specification teaches making of dimethyl ammonium iodide compound of Example 5, regarding " acid addition salts at page 6, lines 7-9, and preparation of "Hydrochloride" is provided in Example 35, page 40, lines 2-5, it does not teach making of the acid addition salt of the ammonium compound(s) of Example 5. Therefore it is very confusing to read the pharmacologically acceptable acid addition salts of the compounds as recited in the claims 1 and 9. Correction is required.

IV. ***Claims Objections***

Claims 7,15,16 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim can not depend from any other multiple dependent claim(s). See MPEP § 608.01(n).

Claims 17-29 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim can not depend from any other multiple dependent claim(s). . See MPEP § 608.01(n).

Claims 26,27 are included in above because they are also improper multiple dependent claims which involve reference to 2 sets of claims. MPEP 608.01(n).

V. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of chronic pain, does not reasonably provide enablement for prophylaxis of functional disorders caused by overstimulation e.g. Alzheimer's disease, Parkinson's disease, degeneration of the cerebellum and other disorders as recited herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims without further experimentation.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: **1)**. The nature of the invention, **2)**. the state of the prior art, **3).** the predictability or lack thereof in the art, **4).** the amount of direction or guidance present, **5)**. the presence or absence of working examples, **6).** the breadth of the claims, and **7).** the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn in part not only to treating but also for prophylaxis of functional disorders caused by overstimulation e.g. diseases such as Alzheimer's disease, Parkinson's disease, degeneration of the cerebellum and others.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat Alzheimer's disease nor is there any compound that can be used to treat brain trauma, Huntington's disease, AD,

Parkinson's disease, amyotrophic lateral sclerosis by a single compound. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites"; chronic pain, neuropathic pain and local anesthesia are covered and diseases that are not treatable pharmacologically are also embraced (e.g. AD, Parkinson's disease, degeneration of cerebellum, Huntington's disease).

3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which are responsive to the activity of voltage dependent sodium channel modulators. There is no evidence of record which would enable the skilled artisan in the identification of the diseases treatable with the disorders claimed herein.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Although specification on page 58 recites dosage for capsules for inhalation, there are no doses present for prophylaxis of the other disorders recited herein.

6) The breadth of the claims: The claims are drawn to disorders that are not related and whose prophylaxis is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following references are cited to show the state of art related to Alzheimer's disease:

- ***Ability of other compounds to dissolve brain deposits in vitro:***

Bush AI (Pub Med Abstract 12689772, also cited as Trends Neurosci. 26/4, 207-14(April 2003)). States that: " Clioquinol inhibits Abeta deposition in the Tg2576 mouse model for AD and could be useful clinically. These insights **could** also apply to other degenerative disorders in which metal-ion protein interactions have been implicated".

- ***Role of clinical evaluation in long-term studies for a potential drug:***

Markstein R (PubMed Abstract 25765520, also cited as Eur. Neurol, 29/3, 33-41(1989)). State that : " It will therefore be of interest to **clinically evaluate in long term studies** the potential of CBM 36-733 to show the progression of neurodegenerative processes".

- ***Role of animal models and its applicability for humans:***

Farber et al (PubMed Abstract 9932393, also cited as Prog. Brain res. 116,421-37(1998)) states that: " In an animal model pharmacological methods have been developed for preventing the overstimulation of these vulnerable corticolimbic

pyramidal neurons and at least some of these methods **may be** applicable for treating AD and schizophrenia".

- ***Studies relating basic pathophysiology and impact of drug on long-term therapy:***

Muller et al(PubMed Abstract 11099718, also cited as J. Neurol. Sci. 181/1-2,98-103(2000)) states that: " Future studies on Parkinsonian subject should discuss their results on the basic pathophysiology or basal ganglia dysfunction in light of a putative impact of long term anti-Parkinsonian drug therapy".

Specification remains silent about any tests or results for prophylaxis of diseases.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claim.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of treating any and all disorders or conditions as recited herein. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been achieved, In re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, Genentech vs. Novo Nordisk, 42 USPQ 2nd

1001, 1006.All available medicines for AD could be used in a limited way, and provide protection mostly in combination with other known agents having many side effects.

VI. *Claim Rejections - 35 U.S.C. § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-8,17,19,21,23,25,26 are rejected under 35 U.S.C. 102(b) as being anticipated by Gennari et al(Tetrahedron Letters, 30/38, 5163-6(1989), also cited as Chemical Abstracts DN113:40077).

Instant compounds of Formula I read on to ref. Gennari in the following way:

R1	= Me;
X	=Oxygen;
A	=-CO-Alkylene-CH(OH)-;
R2/R3/R4	=H;
Phenyl	= Ph-;
-N(R5)(R6)	=-N(Alkyl)2.

Ref. Gennari's Compounds with following CAS RN read on to instant claims.

CAS RN # 127677-18-3 (Benzenepropanoic acid, beta-hydroxy-.alpha.-methyl-,2-(dimethylamino)-1-(2,4,6-trimethylphenyl) ethyl ester.

CAS RN # 127759-16-4 has chemistry similar to CAS RN #127677-18-3, but represents different geometry.

VII. *Claim Rejections - 35 U.S.C. § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinhardt, Klaus et al (J. Med. Chemistry, 27/5,616-27 (1984). Also cited as Chemical Abstract DN 100:174724).

The instant claims are related to Phenyl- and phenylalkyl-substituted ethanolamines and ethylenediamines and treament of neurodegerative disorders, brain trauma, AD, Parkinson's disease and others as recited herein.

The ref. Weinhardt teaches synthesis and utility for central nervous system of 2[(alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines.

The instant claims differ by having additional Me group on 6-position of the phenyl ring wherein 1-position is occupied by -CH(CH2-(NH2(-NH-CH2-Ph).

Compound with CAS RN # 89145-86-8(= 1,2-ethanediamine, 1-(2-methylphenyl)-N 1-(phenylmethyl)-, dihydrochloride) read on the instant claims.

The instant claims differ from the ref. Compound by having the second methyl group on to phenyl ring in 4-position instead of 6-position. See Compound with CAS RN # 89145-99-2(= 1,2-Ethanediamine, 1-(2,5-dimethylphenyl)-N 1-(phenylmethyl)-,dihydrochloride).

Thus, it would have been obvious to one having ordinary skill in the art at the time of invention to prepare instant compounds by modifying or replacing as:

(I). Replacing 6-position H of -CH= of a phenyl ring by alkyl or methyl, and also

(II).Changing the position of Me group from 4- of ref. Weinhardt to 6-position, as claimed herein,

and try out the use/utility as a pharmaceutical by using the conventional chemistry knowledge. The motivation stems from the expectation of making compounds having equal or better medicinal agent.

Analogous alkyl variations would be structurally obvious. See, In re Dillon, 919 F. 2d at 1904. See also Deuel, 51 F. 3d at 1558, 34 U.S.P.Q. 2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify one

compound to obtain another compound(s)"). For example, one compound may suggest its homolog/isomer, because

homolog/isomer often have similar properties, and therefore, chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties, or merely to satisfy their production goals.

Claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F. 2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2141.02.

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obviousness of structurally similar compounds disclosed by prior art" regardless lo the properties disclosed in the inventor's application.

Preliminary search also revealed art ref. Nefzi et al (Tetrahedron 55/2,335-344(1999)). Netzi is referred to because he teaches making of 1,2-propanediamine,N1-[(1S)-2-(methylamino)-1-phenylethyl]phenylethyl- which is a tetrasubstituted

dietnylenetriamine. The instant compounds are tetrasubstituted derivatives of

ethylenediamines, and therefore, the ref. Nefzi is not used.

VIII. ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc. Tech., whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703)308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

BRUCK KIFLE, PH.D.
PRIMARY EXAMINER

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June 1, 2003